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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,952	08/17/2000	Michael S. Kinch	3220-66872	3252

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/640,952	Applicant(s) Kinch et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73, 75-81, 90,* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *72, 73, 75-81, 90, and 91* is/are allowed.

6) ☒ Claim(s) *1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, and 49-69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4, 18,2*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. After review and reconsideration the claims of Group V, drawn to a method of detecting cancer cells, have been re-joined to elected Group I, dawn to a method for detecting metastatic cells.

3. Claims 1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73, 75-81, 90 and 91 are pending and under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action

New Grounds of Rejection

5. Claims 30 and 31 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 3 and 4, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 38 embodies the method of claim 28 wherein the cell population comprises metastatic cancer cells. Claim 28 is dependent upon claim 1 which recites the limitation of detecting the presence of metastatic cells in a cell population. Thus, the limitation of a population comprising metastatic cells is already present in claim 28 by means of dependency on claim 1.

7. Claims 3-7 and 91 are objected to because of the following informalities: Claims 3-7 are dependent upon canceled claim 2 and claim 91 is dependent on canceled claim 82. Appropriate correction is required. For purpose of examination, dependence upon claim 1 will be substituted for dependence upon claim 2.

8. Claims 1-13, 28, 30, 31, 33-46, 90 and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 recites "a method for detecting the presence of metastatic cells in a cell population" as the method objective, but fails to relate the final method step, the detection of antibody-EphA2-binding, to said method objective.

(B) The recitation of "reagent-EphA2-binding" in claim 33 lacks antecedent basis in claim 5.

9. Claims 51 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 51 embodies the method of claim 47 wherein the antibody binds to an extracellular epitope of EphA2. Review of the specification and claims as filed does not find support for the specific limitation of "extracellular" epitope. The specification discusses antibodies to intracellular eptiopes of EphA2 as novel over the prior art, but does not contemplate antibodies to an extracellular epitope of EphA2. This is insufficient to support new claims drawn specifically to method claims reliant upon antibodies which specifically bind to an "extracellular" epitope of EphA2.

6/16/03 RKL

10. Claims 4, 31, 50 and 54 and 81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant has filed a Declaration regarding the deposit of hybridoma cell line producing the antibody D7 of the instant specification, however, applicants declaration is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met for the following reasons.

If the deposits made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposits will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Applicant argues that the deposit of the D7 cell line was made under the Budapest Treaty and that this was stated in the amendment filed March 30, 2002. This is not persuasive, as review of page 2 of said amendment does not mention the Budapest Treaty. Further applicant has failed to make a deposit of the B2D6 cell line, which is required for claim 54. Applicant's declaration is also defective because it does not address points a, b and c, above. The amendment filed March 24, 2003 refers to an Exhibit A containing the contract with the depository, but a review of the file indicates that "Exhibit A" was not attached to the response.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 47, 51, 52, 53, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, are rejected under 35 U.S.C. 102(b) as being anticipated by Khan et al (American Journal of Clinical Pathology, 1984, Vol. 81, pp. 184-191) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675).

Claim 47 is drawn to a method for detecting the presence of metastatic cells in a cell population comprising incubating at least a portion of the cell population with a monoclonal antibody that specifically binds EphA2 to allow binding of the antibody to EphA2, and detecting antibody-EphA2 binding wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population. Claim 51 embodies the method of claim 47 wherein the antibody binds to an extracellular epitope of EphA2. Claim 52 embodies the method of claim 47 wherein antibody-EphA2 binding yields a bound complex comprising a whole cell. Claim 53 embodies the method of claim 52 wherein detecting antibody -EphA2 binding comprises subjecting the bound complex to immunohistochemical staining. Claim 55 embodies the method of claim 47 wherein the bound antibody comprises a detectable label. Claim 47 embodies the method of claim 47 wherein the bound antibody comprises at least one of a fluorescent, chemiluminescent, bioluminescent, enzymatic, chromogenic or radioactive label; and wherein detecting antibody-EphA2 binding comprises detecting at least one detectable label. Claim 57 embodies the method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast, kidney, prostate, lung or colon cells. Claim 58 embodies the method of claim 47 wherein the cell population comprises epithelial cells. Claim 59 embodies the method of claim 47 wherein the cell population comprises cancer cells selected from the group consisting of breast, kidney, prostate, lung and colon cells. Claim 60 embodies the method of claim 47 wherein the cell population comprises epithelial cancer cells. Claim 61 embodies the method of claim 47 wherein the cell population comprises metastatic cancer cells. Claim 62 embodies the method of claim 61 wherein the metastatic cells comprise cancer cells selected from the group consisting of breast, kidney, prostate, lung and colon cells. Claim 63 embodies the method of claim 47 wherein the metastatic cells comprise epithelial cancer cells. Claim 64 embodies the method of claim 47 wherein the cell population comprises cells from a tissue biopsy. Claim 65 embodies the method of claim 64, wherein the tissue comprises breast tissue or prostate tissue.

The abstract of Chen et al discloses that EphA2 is synonymous with Eck.

Kahn et al disclose a method for detecting metastatic cancer cells in a tissue biopsy of breast, kidney, lung and colon cells comprising contacting said cell population with anti-ECK antibodies and visualizing the binding of the antibodies to whole cells by means of immunoperoxidase stating (page 185 to page 186, under the headings of "Pathological Material", "Immunoperoxidase Staining" and Table 1. Khan et al teach that staining with antibody to ECK was indicative of epithelial cancer cells (page 189, second column, third full paragraph) and staining by the anti-ECK antibody was either negative or weakly positive in the main tumor mass, but more strongly positive in areas of infiltration and metastasis (page 189, second column, last full sentence).

13. Claims 1, 3, 5, 11, 21, 23, 28, 30, 33, 35, 37, 38, 40, 41, 45, 47, 49, 52, 55, 56, 58, 60, 61, 63, 64 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Easty et al (International Journal of Cancer, 1995, vol. 60, pp. 129-136) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675) and Lindberg et al (Molecular and Cellular biology, 1990, vol. 10, pp. 6316-6324). The specific embodiments of claims 47, 52, 55, 56, 58, 60, 61, 63, 64 and 68 are set forth above. Claims 49 is drawn to the method of claim 47 wherein the antibody bind to an intracellular epitope of EphA2.

Claim 1 is drawn to a method for detecting the presence of metastatic cells in a cell population comprising the steps of lysing at least a portion of the cell population, incubating the lysed cells with monoclonal antibody that specifically binds to EphA2 to allow antibody binding to EphA2 and detecting antibody-EphA2 binding. Claim 3 embodies the method of claim [1] wherein the epitope of EphA2 is an intracellular epitope. Claim 5 embodies the method of claim [1] wherein the antibody is labeled with a detectable label. Claim 11 embodies the method of claim 1 wherein the incubating and detecting steps comprise Western Blotting methodology. Claim 28 is drawn to the method of claim 1 wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population. Claim 30 is drawn to the method of claim 1

wherein the antibody binds to an intracellular epitope of EphA2. Claim 33 embodies the method of claim 5 wherein the antibody comprises at least one of a fluorescent, chemiluminescent, bioluminescent, enzymatic, chromogenic or radioactive label, and wherein detecting the [antibody]-EphA2 binding comprises detecting at least one detectable label. Claim 35 embodies the method of claim 28 wherein the cell population comprises epithelial cells. Claim 37 embodies the method of claim 38 wherein the cell population comprise epithelial cancer cells. Claim 39 embodies the method of claim 28 wherein the cell population comprises metastatic cancer cells. Claim 40 embodies the method of claim 38 wherein the metastatic cancer cells comprise epithelial cancer cells. Claim 41 embodies the method of claim 28 wherein the cell population comprise cells from a tissue biopsy. Claim 45 embodies the method of claim 28 wherein detecting the antibody-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot and flow cytometry.

Claim 21 is drawn to a method for detecting the presence of metastatic cells in a cell population comprising the steps of incubating the cells with reagent capable of specific binding to a nucleic acid coding for the EphA2 protein and detecting reagent-compound binding. Claim 23 embodies the method of claim 21 wherein the nucleic acid is DNA or RNA.

The abstract of Chen et al discloses that EphA2 is synonymous with Eck.

Easty et al disclose a method for detecting metastatic melanoma cells in a cell population comprising the steps of lysing at least a portion of the cell population, incubating the lysed cells with monoclonal antibody that specifically binds to Eck to allow antibody binding to Eck and detecting antibody-Eck binding by Western blot methodology using chemiluminescence as a detectable label (page 131, under the heading "Immunoblotting analysis"). Easy et al disclose that the anti-Eck antibody was prepared by the method of Lindberg et al (Molecular and Cellular Biology, 1990, Vol. 10, pp. 6316-6324). Lindberg et al disclose that antibodies were raised to the Eck protein by means of a fusion protein comprising the 101 amino acids at the C-terminus of Eck (page 6321, first column, lines 4-7 under the heading "Eck has in vitro kinase activity and

autophosphorylates on tyrosine residues"). Thus, it is inherent in the method of Easty et al that the anti-Ec antibody bound to an intracellular epitope of Eck. Easty et al also disclose a method for detecting the presence of metastatic cells in a cell population comprising the steps of incubating the cells with a probe for Eck mRNA and detecting hybridization between the probe and the mRNA (page 130, under the heading "Northern blotting analysis"). Easty et al further disclose that Eck is expressed at both the protein and the mRNA level in metastatic melanoma cell lines and in sections of metastatic melanomas as indicated by immunohistochemistry (page 135, second column lines 6-13), thus fulfilling the specific embodiments of claims 21 and 23 drawn to reagents which bind to nucleic acids embodiment the EphA2 protein and the specific embodiment of claim 52 drawn to a bound complex comprising a whole cell. Easty disclose that elevated expression of Eck appeared to be correlated with metastasis to epithelial sites such as lung and ileum, rather than to non-epithelial sites such as lymph nodes and cutaneous deposits (page 132, second column, lines 14-19).

14. The rejection of claims 1, 3, 5-13, 21-24, 28-30, 32-47, 49, 51-53, 55-69, 72, 73, 75-81, 90 and 91 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in light of applicants arguments.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 16, 2003